Paediatric prescribing: using unlicensed drugs and medicines outside their licensed indications

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Introduction

Since the late 1960s, laws have been introduced world wide for controlling the provision of medicines. Legislation, which followed the thalidomide disaster, has required that medicines must not be marketed without a license, and that the license should stipulate (amongst other things) for what the product should be used. The thrust of the legislation was directed at drug manufacturers, and expressly permitted doctors and dentists the right to prescribe unlicensed products, or licensed medicines outside their licensed indications (off label). Despite these exemptions, it has always been expected that unlicensed or off-label prescribing should be the exception rather than the rule. For adults, such prescribing is probably unusual. For children, however, prescribing outside a licence is relatively common and, as the report by Impicciatore & Choonara [1] suggests, the position is likely to continue. This editorial reviews paediatric prescribing outside a license and considers its implications and how it might be reduced.

Background

In the UK, licensing legislation was originally introduced through the Medicines Act of 1968. The Act stipulates that a company must not manufacture, promote, sell or supply a medicine, without first obtaining a licence for that product from the UK licensing authority (comprising the UK Ministers of Health) which is advised by the Committee on Safety of Medicines (CSM). Gradually the Act has been subsumed into European Union (EU) legislation and while the principles have changed little, the licence is now referred to as the marketing authorization (MA). Moreover, mechanisms have been introduced for awarding authorization at an EU (central) level, in which case the marketing authority is the European Commission and its advisory body, the Committee for Proprietary Medicinal Products (CPMP).

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To obtain marketing authorization for products in the UK, the company must provide evidence sufficient to persuade the CSM (or the CPMP) that the product will meet satisfactory standards of efficacy, safety, and quality, when used for its specified (licensed) indications. During the licensing process the authority also stipulates what will be contained in information published for prescribers (summary of product characteristics or SPC, formally the data sheet) and for patients (usually as a Patient Information Leaflet or PIL, occasionally on the packet) once the product is available. This information, which forms part of the marketing authorization, sets out the licensed (approved) indications (uses), the dosage regimens to achieve these, plus data such as the product's formulation, constituents, unwanted effects, interactions, warnings and contraindications. Although it is expected that the wording in the SPC and PIL will differ in order to cater for the needs of their different readers, the two must be consistent with one another in terms of the information given.

Current paediatric practice

Notwithstanding the licensing arrangements, evidence from the UK suggests that in children the use of unlicensed medicines or of products for off-label indications is rife, at least in hospitals. In a study involving children in medical and surgical wards, 25% of the products given during the hospital stay were administered for indications for which they were not licensed [2]. In a second study, this time involving children in an intensive care unit, 31% of the prescriptions were for unlicensed or off-label uses [3]. Moreover, since most children were prescribed several products while on the ward (median 3, range 0–26), 70% of the children studied received at least one product outside a licensed indication. While in a third UK study, this time involving 70 neonates treated in intensive care, the proportion of those receiving drugs off-licence was even higher at around 90% [4]. Such prescribing is probably less common in primary care where the incidence is possibly around 10% (Consumers' Association, internal memo following a Drug & Therapeutics Bulletin seminar on 'Prescribing for children outside the licence: is there a problem?' held in July 1998. Mackay C, July 1998).

Types of unlicensed or off-label use

There are four main types of unlicensed or off-label prescribing:

Where a formulation is administered in a way the licence does not intend. Some drugs, for example are given by mouth but have been formulated for use by injection (e.g. dexamethasone injection solution given by mouth to babies) or formulated as tablets but are ground up and given orally as a suspension.

Where proscribed doses are given. Some products are given to children despite specific warnings against, or a stated lack of data on, such use. Dopamine and dobutamine are used in children but their SPCs state that 'safety and efficacy have not been established in children'. Loperamide is given to infants and young children for the treatment of diarrhoea even though the SPC states that its use in children under 4 years of age is contraindicated.

Where drugs or formulations are used without a licence. In this instance products are given that have no UK licence. Sometimes a product, although used for a relatively common condition, may have never been licensed or once had a licence that has since lapsed or been withdrawn. Examples of such products include suspensions of thyroxine and warfarin. Sometimes the drug is licensed in countries outside the EU and has to be imported for use in the UK. Examples of these include thalidomide tablets and Mesna for inhalation. Sometimes products are developed for rare childhood disorders and then it is common for no application to be made for authorization. Betaine, a methyl group donor given to children with homocystinuria, is an example.

Where drugs are used in clinical trials. In this category, products are being evaluated as part of prelicensing clinical trials, and so by definition have yet to be awarded a licence. These trials are usually sponsored by the manufacturer and will only be undertaken with the approval of the Medicines Control Agency (MCA). Often prescribing is continued after the study is over and before the licence is awarded, in these circumstances prescribing is similar to the category described in the previous paragraph.

Is there a problem?

While there is nothing illegal about prescribing drugs that are unlicensed or used in ways not specified in the licence, the clinical and ethical dilemmas such prescribing raises provide a powerful argument for curtailing the practice wherever possible.

The licensing arrangements ensure a rigorous assessment of each medicine, using volumes of data (collected over perhaps 10–12 years), on the efficacy and safety of the product when used for a given indication. Tight controls are set on the quality of the product, and when it is given according to the recommendations in the SPC the authority calculates that it is more likely to improve patient wellbeing than do harm. The recommendations are set against knowledge of the type of patient likely to be given the medicine and the disease being treated. While the licensing system has its limitations (efficacy relative to other drugs, for example, is not a criterion up for consideration), the underlying principles are sound. Moreover, the information set out in the product's SPC and the PIL provides a written basis for understanding by the prescriber and a basis for discussion between prescriber and patient when they are considering treatment options.

When a medicine is prescribed outside these arrangements, this support is absent and treatment tends to based less on published information and more on assumptions and extrapolations. The validity of such an approach is questionable because there are such great differences between adults and children, and even between children of different ages, with regard for instance to the pharmacodynamic and pharmacokinetic responses to drugs, the types and natural histories of illnesses that can present, and the effects of drugs on normal growth and development (for examples see 'Notes for Guidance on Clinical Investigation of Medicinal Products in Children' Published by the European Agency for the Evaluation of Medicinal Products, Human Resources Unit, March 1997). Similarly it would be unwise to ignore the number of unknowns introduced when, say, a solution or suspension is given orally instead of as the original tablet formulation. Without the quality and quantity of data needed to satisfy the standards required of the licensing process, it is unlikely that these concerns will be resolved in a systematic fashion. There is therefore the prospect of medicines being given inappropriately, perhaps in suboptimal doses, and with children deprived of potential advantages or being put at unnecessary risk.

All these issues are relevant at the time of prescribing, but the licensing arrangements have another, longer-term, dimension. Once a drug is marketed, the MCA closely tracks the product's unwanted effects in a process that relies heavily on spontaneous reporting by prescribers (as with the Yellow Card System) and on data collected in postmarketing surveillance by the manufacturer. If an unlicensed drug is used, or a licensed one used off label, these mechanisms are undermined since responsibilities for collecting and collating data have no defined framework. Consequently, spontaneous reporting is uncommon (in the event of mishap prescribers may be frightened to admit they have prescribed outside a licence), it is not clear whether

either the CSM or the company have a duty to pursue such reports, and it is difficult to know what should be done about the information since there may be little or no scope for modifying published information in the form of a revised SPC or PIL. For all these reasons, medical practice is deprived of the usual ways of minimising problems for the future.

The ethical issues raised by prescribing unlicensed products or medicines off label are also serious. Increasingly, patients are expected to be involved in decision-making about management, and this holds for children (and their parents) as it does for adults. Clearly, the mechanics of obtaining valid consent in adults and those aged under 16 years are different, and will vary further depending on the age of the child, but to deprive (albeit inadvertently) this set of patients important basic information, in the form of a PIL, means that they are likely to be disenfranchised. In other words—they are essentially discriminated against. But even if written material is provided by a physician or pharmacist in some *ad hoc* way, the depth and reliability of the material used to produce such information is most unlikely to match that used in support of the licence. This imbalance makes consent offered by children and/or their parent(s) less secure. In these circumstances it is best for the prescriber to explain the position to the child and/or parent [5], informing them of the significance of using a drug without, or outside the terms, of a licence. Although this does not rectify the problem, and might even inhibit prescribing, it should help resolve the ethical issues surrounding the validity of consent.

What is to be done?

While there is no systematic evidence that children are disadvantaged by the high levels of unlicensed or off-label prescribing, it seems inevitable that they are. The first step in resolving the problem is to acknowledge its existence. The second, is for all those involved in it to share responsibility for its resolution. To this end there has been a joint enquiry by the British Paediatric Association and The Association of the British Pharmaceutical Industry [6], and, more recently, the issue was tackled by the House of Commons Health Select Committee [7]. Similar enquiries have now been undertaken in Australia and Canada [6], the USA [8] and also by the EU [9].

So far, the greatest steps to rectify matters seem to have come from the regulators, with recommendations for changes to be made in licensing requirements by, for instance, the Food and Drug Administration (FDA) in the USA [8] and the European Medicines Evaluation Agency (EMEA) in the EU [9]. In these reports, the authorities define the problem and press the manufacturing companies to provide detailed data for prescribing in children whenever the product is likely to be used for them (data, rather than disclaimers or lacunae, are called for). They also urge the companies to develop the formulations needed to administer the products satisfactorily. The ultimate goal is to widen the licensed indications and provide the necessary advice to cover all aspects of paediatric prescribing. With these, it is inevitable that the unlicensed use of medicines in children will fall and the value of the revised SPCs and PILs will be enhanced.

New research will be required in order to meet these goals, and the extent of the research that will be needed can be gauged from the EU's request to companies to target developments relevant to the needs of five different age groups. The age bands are [9]:

Pre-term new-born infants (born at less than 36 weeks of gestation)

Term new-born infants (age 0–27 days)

Infants and toddlers (age 28 days to 23 months)

Children (age 2–11 years)

Adolescents (age 12–17 years).

The recommendations also define the sorts of products for which data and formulations are needed, and outline what information is required. There are four product categories; these cover medicinal products intended for treating diseases:

affecting children exclusively;

mainly affecting children, or which are of particular gravity in children, or have a different natural history in children;

occurring in adults and children, for which there is currently no treatment;

occurring in adults and children, for which other treatment exist.

These EU recommendations, which came into operation in September 1997, were based on discussions that began formally in October 1995. The report by Impicciatore & Choonara [1] is important as it provides details of actual practice in EU licensing as it relates children during much the same period (January 1995 to April 1998). The study was based on a review of the European Public Assessment Reports (EPARs) published by the European Medicines Evaluation Agency (EMEA; equivalent to the UK MCA) during the 40-month period. These reports, which accompany all products licensed by the central (EU) scheme, give details of the basis for the marketing authorization approval and include the text of the product's SPC and PIL. Of the 45 new substances licensed, 29 (64%) were of possible use in children but only 10 were licensed for paediatric use. Of the 19 products without a paediatric licence, the SPCs of 9 advised readers that use of the product in children had not been established. These findings

provide a baseline for assessing change; they also reinforce how important it is for changes to take place. They also raise questions about whether the EMEA, if left to work in isolation, can implement the changes it itself recommends.

Conclusion

Medicines prescribed for children should, wherever possible, be licensed and used according to licensed indications. The current widespread use of products outside these conditions disadvantages children, and is unacceptable. Reducing the need for unlicensed or off-label prescribing will require extensive, and costly, trials. These requirements were inevitable and should not necessarily be taken to reflect a new burden, but more to reveal the price of neglecting the needs for thorough assessments of medicines in the past. Trials in children are fraught with problems and are particularly difficult to undertake in very sick children or in children with diseases that are rare. It is crucial to avoid studies that are poorly designed or run, as these cannot provide useable results. To this end, it would be appropriate for those undertaking studies to establish the close involvement of paediatric clinical pharmacologists. Ultimately, the changes needed to produce improvement will require co-operation between legislators, physicians, industry and consumers alike.

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